EXTERNAL SEMINAR

NEUROCHLORE - INMED Conference

INMED Conference Room

Monday, 17th October 2016 - 11 a.m.

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Invited by: Dr. Yehezkel BEN-ARI

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Vulnerable developmental periods in Kv7/M and HCN/h channelopathies in mice

The developing nervous system is especially vulnerable during critical developmental time windows, when insults may be more likely to produce long-term consequences, including neurological diseases, such as epilepsy. During the last years, we have investigated the developmental effects of channelopathies in mice using a transgenic strategy designed to reversibly inactivate Kv7/M- or HCN/h-channel-mediated currents at different developmental stages. Kv7 and HCN subunits are linked to neonatal epileptic encephalopathy in humans, and we have used dominant-negative (DN) subunits to induce functional knockouts that are independent of the expressed endogenous subunits. Depending on the developmental period of M- or h-current suppression, we observed distinct phenotypes. Mice with dominant-negative Kv7 subunits expressed in early postnatal development were hyperactive, prone to seizures, exhibited abnormal hippocampal morphology and neuroinflammation, and increased network and unit activities. The development of this phenotype was prevented by temporarily blocking transgene expression, or by prophylactically treating the animals with bumetanide. Both approaches were restricted to the first two postnatal weeks.

Transgenic suppression of HCN/h-currents induced development-specific distinct phenotypes. Early prenatal ablation of HCN/h currents in mouse forebrain resulted in a severe microcephaly phenotype. In contrast, early postnatal suppression of HCN-channel activity did not affect the brain structure, but resulted in behavioral abnormalities. HCN-DN mice displayed delayed somatosensory development, cognitive deficits in working memory and spatial learning and memory, hyperactivity, and altered neonatal network activity.

These results collectively suggest that, in Kv7 or HCN channelopathies, interventions timed to specific vulnerable windows of brain development may be able to prevent or arrest disease progression.

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